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**O. V. Tkachova, M. Allaberdiev**

National University of Pharmacy

## THE CLINICO-ECONOMIC ANALYSIS OF PHARMACOTHERAPY IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NASH) have become the most common liver diseases in the world.

**Aim.** To conduct the clinico-economic analysis of pharmacotherapy in patients with NASH, who underwent treatment in one of the healthcare institutions of Kharkiv in 2013.

**Materials and methods.** The study materials were case histories of patients and such regulatory documents of the Ministry of Health of Ukraine as the State Formulary (SF) of Medicines of Ukraine (2013), methodological recommendations on the diagnosis and pharmacotherapy of the digestive system diseases (2007), the Unified Clinical Protocol (UCP) "Non-alcoholic steatohepatitis" (Order No. 826 dated November 6, 2014). The pharmacoeconomic methods used were ABC, VEN and frequency analyses.

**Results.** The results of the study demonstrated that the pharmacotherapy of patients with NASH complied with the main requirements specified in the Ukrainian Methodological Recommendations (2007), but did not meet the requirements of the NASH UCP by the approaches of the pathogenetic therapy prescribed. The results of "formal" VEN analysis showed that most drugs prescribed (76 %) were classified as group V – vital drugs since they were present in the SF of Ukraine. A predominant portion (83.2 %) of costs associated with the pharmacotherapy in patients with NASH was spent on these drugs. However, 16.8 % of the costs spent on 24 % of drugs, which are absent in the SF, indicates the need for further correction of the NASH pharmacotherapy in the healthcare institution under study.

**Conclusions.** The pharmacotherapy of patients with NASH in the healthcare institution of Kharkiv is rational from clinical and economic point of view, but requires further correction in accordance with the SF and the new UCP for NASH.

**Key words:** non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; medical regulatory documents; clinico-economic analysis

**O. B. Ткачова, М. Аллабердієв**

Національний фармацевтичний університет

### Клініко-економічний аналіз фармакотерапії хворих на неалкогольний стеатогепатит

Неалкогольна жирова хвороба печінки та неалкогольний стеатогепатит (НАСГ) стали найпоширенішими захворюваннями печінки в усьому світі.

**Мета роботи.** Проведення клініко-економічного аналізу фармакотерапії у пацієнтів з НАСГ, які проходили лікування в одному із закладів охорони здоров'я (ЗОЗ) м. Харкова у 2013 році.

**Матеріали та методи.** Матеріалами служили історії хвороб та нормативні документи МОЗ України: ДФЛЗУ (2013 р.), методичні рекомендації з раціональної діагностики та фармакотерапії захворювань органів травлення (2007 р.), уніфікований клінічний протокол (УКП) «Неалкогольний стеатогепатит» (наказ № 826 від 6.11.2014 р.). Використані фармакоеконімічні методи: ABC, VEN та частотний аналіз.

**Результати.** За результатами дослідження встановлено, що фармакотерапія хворих з НАСГ за призначуваними напрямками патогенетичної терапії відповідала основним вимогам, зазначеним в українських методичних рекомендаціях (2007 р.), але не відповідала вимогам УКП НАСГ. За результатами «формального» VEN-аналізу встановлено, що переважна більшість призначуваних ЛЗ (76 %) була віднесена до групи V – життєво важливих, оскільки була наявна в ДФЛЗУ. На них витрачена домінуюча частина грошових коштів (83,2 %), пов'язаних з фармакотерапією хворих з НАСГ, але 16,8 % коштів, витрачених на 24 % ЛЗ, відсутніх в ДФЛЗУ, вказують на необхідність подальшої корекції фармакотерапії НАСГ в даному ЗОЗ.

**Висновки.** Фармакотерапія пацієнтів з НАСГ в ЗОЗ м. Харкова є раціональною з клінічної та економічної точок зору, але потребує подальшої корекції фармакотерапії відповідно до ДФЛЗУ та до нового УКП НАСГ.

**Ключові слова:** неалкогольна жирова хвороба печінки; неалкогольний стеатогепатит; медико-нормативні документи; клініко-економічний аналіз

**O. B. Ткачова, М. Аллабердієв**

Национальный фармацевтический университет

### Клинико-экономический анализ фармакотерапии больных с неалкогольным стеатогепатитом

Неалкогольная жировая болезнь печени и неалкогольный стеатогепатит (НАСГ) стали распространенными заболеваниями печени во всем мире.

**Цель работы.** Проведение клинико-экономического анализа фармакотерапии у пациентов с НАСГ, проходивших лечение в одном из учреждений здравоохранения (УЗ) г. Харьков в 2013 году.

**Материалы и методы.** Материалами служили истории болезней и нормативные документы Минздрава Украины: ГФЛСУ (2013 г.), методические рекомендации по рациональной диагностике и фармакотерапии заболеваний органов пищеварения (2007 г.), Унифицированный клинический протокол (УКП) «Неалкогольный стеатогепатит» (приказ № 826 от 6.11. 2014 г.). Использованы фармакоэкономические методы: ABC, VEN и частотный анализ.

**Результаты.** По результатам исследования установлено, что фармакотерапия больных с НАСГ по назначаемым направлениям патогенетической терапии отвечала основным требованиям, указанным в украинских методических рекомендациях (2007 г.), но не отвечала требованиям УКП НАСГ. По результатам «формального» VEN-анализа установлено, что большая часть назначаемых ЛС (76 %) была отнесена к группе V – жизненно важных, поскольку присутствовала в ГФЛСУ. На них потрачена доминирующая часть денежных средств (83,2 %), связанных с фармакотерапией больных с НАСГ, но 16,8 % средств, израсходованных на 24 % ЛС, отсутствующих в ГФЛСУ, указывают на необходимость дальнейшей коррекции фармакотерапии НАСГ в данном УЗ.

**Выводы.** Фармакотерапия пациентов с НАСГ в УЗ г. Харькова является рациональной с клинической и экономической точек зрения, но требует дальнейшей коррекции в соответствии с ГФЛСУ и новым УКП НАСГ.

**Ключевые слова:** неалкогольная жировая болезнь печени; неалкогольный стеатогепатит; медико-нормативные документы; клинико-экономический анализ

Over the last decades, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have become the most common liver diseases in Western countries, they range from 27 % to 38 % [1, 2]. Non-alcoholic steatohepatitis is a progressive form of NAFLD, which is accompanied with inflammation and fibrosis of the liver. The basic mechanism of the NAFLD development is the metabolic syndrome, which primarily develops in overweight patients. Insulin resistance, hypertension and the oxidative stress prevail in the pathogenesis of NAFLD [3]. The studies have proven that patients diagnosed with NASH are at high risk of developing cirrhosis and hepatocellular carcinoma (HCC), which reaches up to 30 % over 10 years after the disease onset [4-6]. Currently, HCC is the sixth most common type of cancer in the world and the third leading cause of death from cancer [7]. The above-mentioned facts demonstrate the need of measures for early prevention of NASH and NAFLD, and when diagnosing – for an effective pharmacotherapy of these diseases.

The pharmacoeconomic analysis of the NASH therapy has become a subject of the research conducted by foreign scientists [1, 8-10]. These works present the results of the studies performed using the “cost-effectiveness” and “cost-utility” methods, as well as data on costs for the treatment of NASH. The treatment of patients suffering from NASH and NAFLD is associated with significant costs. For example, in the healthcare system of Iran the total costs for NAFLD pharmacotherapy in adult population exceed 1 billion dollars a year [10]; in the US, according to the five-year studies, healthcare costs have increased by 26 % due to the increase in the number of the overweight population and the incidence of NAFLD [1].

Until 2014 to make a diagnosis and perform the rational treatment of NASH physicians in Ukraine used the methodological recommendations by O. Ya. Babak and N. V. Kharchenko “The rational diagnosis and pharmacotherapy of diseases of the digestive system: methodological recommendations” (2007) [11]. In 2014 the Unified Clinical Protocol (UCP) of the

Primary, Secondary (Specialized) Medical Care “Non-alcoholic steatohepatitis” was approved by the Order of the Ministry of Health of Ukraine No. 826 dated November 6, 2014. It is based on the principles of evidence-based medicine taking into account the results of studies of the best world practices. In accordance with this medico-technological document (MTD) the basic method for treating NASH and preventing serious complications is modification of the diet and life style, as well as the pharmacotherapy targeted at stopping and reducing the impact of such risk factors as insulin resistance, dyslipidemia, obesity and the metabolic syndrome [12].

The search for recent scientific publications and pharmacoeconomic studies conducted in Ukraine has shown that there are no current statistical data on the NASH prevalence, as well as no publications concerning analysis of quality of the NASH therapy in accordance with MTD recommended by the Ministry of Health of Ukraine (MOH), such as the State Formulary (SF) of Medicines of Ukraine and the UCP of the Primary, Secondary (Specialized) Medical Care of Patients with NASH. The above-mentioned facts demonstrate the necessity for assessment of drug prescribing to patients with NASH, and it will promote optimization of both the pharmacotherapy itself and its costs.

The aim of this work is to give the comprehensive assessment of the drug consumption and the rationality of the pharmacotherapy in patients with NASH, who underwent treatment in one of the healthcare institutions of Kharkiv in 2013, by analyzing the therapy compliance with the current MTD based on the results of clinico-economic analysis of the SF of Ukraine (the 5th edition, 2013) [13], the Ukrainian methodological recommendations on the diagnosis and pharmacotherapy of the digestive system diseases (2007) [11] and the UCP of the Primary, Secondary (Specialized) Medical Care of patients with NASH (2014) [14].

## Materials and Methods

For this purpose the following objectives should be performed: to carry out the retrospective analy-

**Principles of treatment of NASH**  
(According to the Methodological Recommendations by Babak O. and Kharchenko N. (2007, Ukraine)  
and the American Association for the Study of Liver Diseases (2012))

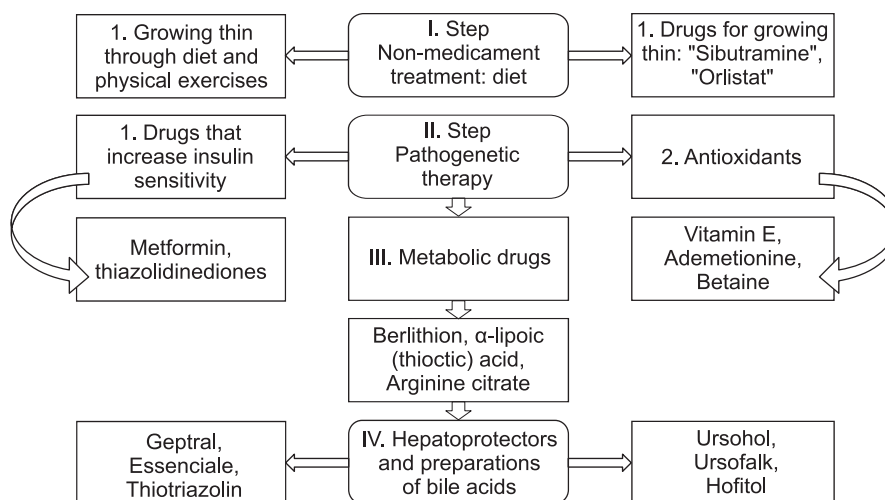


Fig. Principles of the NASH treatment before introduction of the UCP by the MOH of Ukraine (2014)

sis of medication administration records of patients with NASH; to determine the frequency of prescribing drugs to patients with NASH; according to the results of "formal" VEN analysis in order to assess the therapeutic quality based on the presence of prescribed drugs in the annually revised medical regulatory document – the State Formulary of (SF) Medicines of Ukraine (the 5th edition, 2013) [13]; to assess compliance of the NASH therapy approaches with the requirements of the Ukrainian Methodological Recommendations (2007) [11] and with the NASH UCP (2014) [14]; to determine the structure and rationality of costs for the NASH therapy according to the ABC analysis results [15]. When determining the cost of the treatment course with drugs prescribed to patients with NASH the average retail price for these drugs was used as of May 2015 [16].

## Results and Discussion

According to the Ukrainian Methodological Recommendations (2007) [11] been in effect before introduction of the UCP for NASH treatment the following basic principles can be identified (Fig.).

With introduction of the UCP the recommendations for the life style modification have remained valid, but with updated data regarding the physical activity and the body weight loss ( $BMI < 25 \text{ kg/m}^2$ ), while approaches to the NASH pharmacotherapy have changed due to the clinical studies performed with the results based on the data of evidence-based medicine [9].

To date, the following drugs should be prescribed for the NASH pharmacotherapy in accordance with the UCP:

1. Tocopherol (Vitamin E) in a daily dose of 200-400 mL (only in patients with biopsy-proven NASH, without diabetes mellitus).

2. Omega-3 fatty acids, metformin and pioglitazone that should be used only for correction of concomitant metabolic disorders.

3. Metabolic drugs with the proven efficacy: L-carnitine, lecithin, choline, B vitamins, especially B1, B6, B12, and folic acid.

The UCP for the NASH treatment that came into effect after its approval by the MOH of Ukraine from November 6, 2014 [14] contains no information regarding prescription of hepatoprotectors and drugs with ursodeoxycholic acid. It indicates their unproved efficacy for this pathology.

The results of the retrospective analysis of case histories showed that 54 patients (30 males (56 %) and 24 females (44 %) aged from 20 to 85 years) diagnosed with non-alcoholic steatohepatitis underwent treatment in the Kharkiv healthcare institution during 2013. The average duration of staying of one patient in the hospital was 14 days. In addition to the main diagnosis of NASH, the majority of patients had concomitant diseases; chronic pancreatitis (33 %) and cholecystitis (43 %) were the most common.

To treat 54 patients 74 drugs were prescribed, including 51 drugs for the treatment of concomitant diseases and 23 drugs for the NASH treatment. The total costs for pharmacotherapy of 54 patients with NASH were 100,376.44 UAH. On average 1,859 UAH were spent on the treatment course per a patient. Over the period examined 355 prescriptions of drugs to patients with NASH were recorded in the healthcare institution studied. It is on average 6.6 drugs per a patient, and indicates the presence of polypragmasy and the need to reduce the number of prescriptions to 4-5.

The first stage of our work included frequency analysis, on its basis top-10 leaders were determined by the number of prescriptions. A half of these top-10

Table

**Comparison of frequency and VEN-analyses with drugs of group A  
for treating non-alcoholic steatohepatitis**

No.	Trade name of a drug	How supplied	Average retail price per a pack, UAH	Frequency of prescription	Cost of the drug per the treatment course, UAH	% of the total costs	SF of Ukraine, (the 5th edition, 2013)
1	Berlithion	soln. for inj., 2 mL, ampl. No.5	680.29	18	19431.72	19.35	V
2	Heptral	soln. for inj., 5 mL, ampl. No.5	197.31	7	13365.8	13.31	V
3	Phosphogliv	vial, 2.5 g, i.v., No.5	369.21	16	11685.12	11.64	N
4	Espa-lipon	soln. for inj., 5 mL, ampl. No.5	57.26	9	6667.92	6.64	V
5	Thiotriazolin	soln. for inj., 4 mL, ampl. No.5	94.98	31	4767.18	4.74	V
6	Duspatalin	caps., 200 mg, No.30	103.36	23	4735.16	4.71	V
7	Ursochol	soln. for inj., 2 mL, ampl. No.10	247.95	19	2742.09	2.73	V
8	Spasmobru	caps., 200 mg, No.30	310.09	35	2704.07	2.69	V
9	Dalargin	caps., 250 mg, No.50	563.70	13	2467.60	2.45	V
10	Essentiale N	soln. for inj., 2 mL, ampl. No.10	254.94	6	2272.77	2.26	V
11	Sodium Chloride	soln. for inj., 0.9 %, 200 mL	151.63	26	2262.0	2.25	V
12	Reamberin	soln. for inj., 200 mL, vial	140.10	4	1794.52	1.78	V
13	Creon 10,000	caps., 150 mg, vial, No.50	73.24	15	1430.35	1.42	V
14	Traumeel S	soln. for inj., 2.2 mL, No.5	707.73	5	1412.45	1.40	N
15	Ursofalk	caps., 500 mg, No.50	135.95	5	1251.95	1.24	V
16	Heptral	tabl., 400 mg, No.20	189.69	2	1231.61	1.23	V

leaders (Thiotriazolin, Ursochol, Berlithion, Phosphogliv, Espa-lipon) was prescribed to patients with NASH within combined therapy regimens, and other drugs were used for the therapy of concomitant diseases.

In 2013 during the NASH treatment the prescription of hepatotropic agents Thiotriazolin (Galychfarm) and Ursochol (Darnytsia) met the Methodological Recommendations applicable at that time (2007). However, at present this approach to the pharmacotherapy of patients with NASH does not meet the current UCP (2014). It should be also noted that among the metabolic drugs prescribed for the NASH pharmacotherapy the leading positions were occupied by Berlithion and Espa-lipon corresponding to the pharmacotherapy approaches that were applicable at the time of the study. Such metabolic drugs recommended by the UCP for the NASH treatment as L-carnitine, lecithin, choline and B vitamins (except for prescription of a combined drug Neurobion to one patient) were prescribed to none of the patients. Thus, predominant approaches to the NASH pharmacotherapy met the requirements applicable at the time of the study, but were not consistent with the new UCP.

The next stage of our work included the assessment of the rationality of costs based on the results of ABC analysis, which comprised distribution of drugs into three groups by their cost. According to

the estimates obtained group A consisted of 16 drugs with the total costs of 79.84 %, and 80,140.55 UAH by the absolute value. Group B contained 23 drugs with the costs of 15.01 % (15,066.50 UAH). Group C included 35 drugs with the costs of 5.15 %, (51,69.39 UAH).

Drugs of group A are the most cost-intensive and of primary interest when analyzing the results obtained. Table presents distribution of costs for drugs of group A by trade names (TN). Five leaders of group A by costs included drugs for pathogenetic and symptomatic therapy of NASH – hepatoprotectors Heptral and Phosphogliv, antioxidant Thiotriazolin, as well as drugs affecting metabolic processes (Berlithion and Espa-lipon); 55.68 % of the total amount of costs was spent on them. Therefore, most costs from group A were spent on drugs for the NASH treatment. The first leader in the ABC ranking by TN was the metabolic drug Berlithion containing alpha lipoic acid (Berlin-Chemie/Menarini Group, Germany) – 19.35 % of the total amount of costs (79.84 %). It was prescribed to 18 patients and had the highest price per a pack and per a treatment course. This drug was prescribed to NASH patients suffering from concomitant diabetic polyneuropathy.

To determine how rational money was spent on the NASH treatment VEN analysis performed in accordance with the SF (the 5th edition, 2013)



became an essential study component. The results obtained demonstrated that 76 % (56 drugs) of all drugs prescribed received the index “V” and were classified as vital, and 24 % (18 drugs) were not included in the SF; they had the index “N” and the status of non-essential drugs. Non-essential drugs include such drugs of the metabolic action as Co-carboxyd, Mildronate, Neurobion, Smart Omega and Thiotriazolin; antacids Mucogen and Gaviscon; antispasmodic agents Spasmomen and Spasmalgin; probiotics Biolact and Lacium; an anticholinergic agent Tribudat; a combined anti-inflammatory homeopathic medicinal product Traumeel S; a nootropic agent Cavinton; a capillary stabilizer L-Lysine Aescinat; a hepatotropic drug Phosphogliv; a drug Furamag used in urology; and a dietary supplement Lactofiltrum that promotes normalization and maintenance of the normal intestinal microflora. Costs for 18 drugs from category “N” were 16,807.4 UAH (16.8 % of the total amount of costs). These drugs were prescribed to 37 patients (4.8 % of all prescriptions).

Comparison of the results of frequency and “formal” VEN analyses showed that 9 out of 10 leaders by the number of prescriptions are classified as vital drugs (Thiotriazolin, Spasmobru, Duspatalin, Sodium Chloride, Berlithion and Ursochol, Espa-lipon, Dalargin, Creon 10,000) since they are included in the SF (the 5th edition). Only the hepatotropic drug Phosphogliv manufactured by Pharmstandard is a non-essential drug as it has the insufficient evidence base and is not included in the SF (the 5th edition).

According to the results of ABC/VEN analysis 87.5 % of drugs in group A (14 out of 16 drugs) were referred to the index “V” (vital drugs) (Tab.). The SF did not contain the abovementioned hepatotropic drug Phosphogliv and the homeopathic medicinal product Traumeel S manufactured by Heel (Germany). It is associated with the low evidence base of their efficacy. The results of ABC/frequency

analysis demonstrated that the major costs were spent on frequently prescribed drugs: drugs of group A were prescribed 234 times, and it was more than a half (65.9 %) of all prescriptions.

Thus, comparison of the results of ABC, VEN and frequency analyses indicated that the main approaches to the therapy of patients with NASH complied with the clinical recommendations (2007) applicable at the time of the study, but did not meet the requirements of the NASH UCP (2014). A small number of prescriptions and an insignificant part of costs were associated with non-essential drugs that were not included in the SF (2013). Therefore, in general, the actual pharmacotherapy of patients with NASH in the Kharkiv healthcare institution is rational from clinical and economic point of view, but requires further correction in accordance with the SF of Ukraine and the new UCP.

### CONCLUSIONS

1. The pharmacotherapy of patients with NASH has complied with the main requirements specified in the Ukrainian Methodological Recommendations on the diagnosis and treatment of the digestive system diseases (2007), but it has not met the current requirements of the NASH UCP (2014) by the approaches of the pathogenetic therapy prescribed. It requires further correction of drug prescription in the healthcare institution studied taking into account the new medico-technological document of the MOH of Ukraine.

2. According to the results of ABC/VEN analysis a predominant portion (82 %) of the total costs for the pharmacotherapy was spent on drugs included in the SF of the 5th edition (76 %). However, 16.8 % of the costs spent on 24 % of drugs, which are absent in the SF, indicates the need for further correction of the NASH pharmacotherapy in the given healthcare institution.

**Conflicts of Interest:** authors have no conflict of interest to declare.

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Відомості про авторів / Information about authors / Информация об авторах

**Ткачова О. В.**, доктор фармацевтичних наук, доцент кафедри фармакоэкономики, Національний фармацевтичний університет  
**Tkachova O. V.**, Doctor of Pharmacy (Dr. habil.), associate professor of the Department of Pharmacoeconomics, National University of Pharmacy

**Ткачова О. В.**, доктор фармацевтических наук, доцент кафедры фармакоэкономики, Национальный фармацевтический университет  
**Аллабердиев М.**, магистрант кафедры фармакоэкономики, Национальный фармацевтический университет  
**Allaberdiev M.**, master's degree student of the Department of Pharmacoeconomics, National University of Pharmacy  
**Аллабердиев М.**, магистрант кафедры фармакоэкономики, Национальный фармацевтический университет  
Адреса для листування: 61168, м. Харків, вул. Валентинівська, 4, кафедра фармакоэкономики НФаУ. Тел. (0572) 65-88-95.

E-mail: [tkachevaov@gmail.com](mailto:tkachevaov@gmail.com)

Mailing address: 4, Valentynivska str., Kharkiv, 61168, Ukraine, Department of Pharmacoeconomics, National University of Pharmacy.

Tel. (0572) 65-88-95. E-mail: [tkachevaov@gmail.com](mailto:tkachevaov@gmail.com)

Адрес для переписки: 61168, г. Харьков, ул. Валентиновская, 4, кафедра фармакоэкономики НФаУ. Тел. (0572) 65-88-95.

E-mail: [tkachevaov@gmail.com](mailto:tkachevaov@gmail.com)